Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

(It is noted that double underlining is utilized to indicate underlining in original claims)

Listing of Claims

1. (currently amended): A knockin ~~non-human~~ gene-mutated ~~animal~~ mouse having a mutant presenilin-1 gene, wherein the mutant presenilin-1 gene results in overexpression of Amyloid β 42 in the brain of said mouse.

2. (original) The gene-mutated animal according to claim 1, wherein the animal has a mutant presenilin-1 gene which comprises a DNA having a sequence encoding a presenilin-1 protein in which an amino acid in the amino acid sequence of the presenilin-1 protein is substituted with a different amino acid.

3. (withdrawn-currently amended): A knockin ~~non-human~~ gene-mutated ~~animal~~ mouse having a mutant presenilin-1 gene which comprises a DNA having a sequence encoding a mutant presenilin-1 protein which has an amino acid sequence in which one or more amino acids at positions selected from the group consisting of amino acids numbers 79, 82, 96, 115, 120, 135, 139, 143, 146, 163, 209, 213, 231, 235, 246, 250, 260, 263, 264, 267, 269, 280, 285, 286, 290, 318, 384, 392, 410, 426 and 436 is substituted with different amino acids in the amino acid sequences of presenilin-1 protein, wherein the mutant presenilin-1 gene results in overexpression of Amyloid β 42 in the brain of said mouse.

4. (withdrawn-currently amended): A knockin ~~non-human~~ gene-mutated ~~animal~~ mouse having a mutant presenilin-1 gene which comprises a DNA having a sequence encoding a mutant presenilin-1 protein which has one or more mutations selected from the group consisting of A79V, V82L, V96F, Y115H, Y115C, E120K, E120D, N135D, M139V, M139T, M139I, I143F, I143T, M146L, M146V, H163Y, H163R G209V, I213T, A231T, A231V, L235P, A246E, L250S, A260V, C263R, P264L, P267S, R269G, R269H, E280A, A285V, L286V, S290C, E318G, G384A, L392V, C410Y, A426P and P436S in the amino acid sequences of presenilin-1 protein, wherein each alphabet represents an amino acid expressed as a one-letter symbol, each number represents an amino acid number from the n-terminus of the presenilin-1 protein, and the descriptions means that a wild-type amino acid shown in the left of the number is substituted with an amino acid shown on the right, wherein the mutant presenilin-1 gene results in overexpression of Amyloid β 42 in the brain of said mouse.

5. (currently amended): A knockin ~~non-human~~ gene-mutated ~~animal~~ mouse having a mutant presenilin-1 gene which comprises a DNA having a sequence encoding a mutant presenilin-1 protein in which isoleucine at position 213 of a presenilin-1 protein is substituted with an amino acid other than isoleucine, wherein the mutant presenilin-1 gene results in overexpression of Amyloid β 42 in the brain of said mouse.

6. (currently amended): A knockin ~~non-human~~ gene-mutated ~~animal~~ mouse having a mutant presenilin-1 gene which comprises a DNA having a sequence encoding a mutant presenilin-1 protein in which isoleucine at position 213 of a presenilin-1 protein is substituted

with threonine, wherein the mutant presenilin-1 gene results in overexpression of Amyloid β 42 in the brain of said mouse.

7. (currently amended): The non-human gene-mutated ~~animal~~ mouse according to claim 1, wherein the ~~animal~~ mouse has the mutant presenilin-1 gene wherein a DNA sequence encoding around an amino acid at position 213 in an amino acid sequence of the presenilin-1 protein is mutated to the following sequence:

5'-TGTGGTCGGGATGATMGCC ANC CACTGGAAAGGCCC-3'

wherein N represents a base other than T, M represents T or C, and the underlined bases encode the amino acid at position 213.

8. (currently amended): The non-human gene-mutated ~~animal~~ mouse according to claim 1, wherein the ~~animal~~ mouse has the mutant presenilin-1 gene wherein a DNA sequence encoding around an amino acid at position 213 in an amino acid sequence of the presenilin-1 protein is mutated to the following sequence:

5'-TGTGGTCGGGATGATMGCC ANC CACTGGAAAGGCCC-3'

wherein N represents C, M represents T or C, and the underlined bases encode the amino acid at position 213.

9. (currently amended): The non-human gene-mutated ~~animal~~ mouse according to claim 1, wherein the ~~animal~~ mouse has the mutant presenilin-1 gene wherein a DNA sequence encoding around an amino acid at position 213 in an amino acid sequence of the presenilin-1 protein is mutated to the following sequence:

5'-TGTGGTCGGGATGATMGCC XYZ CACTGGAAAGGCCC-3'

wherein XYZ represents a codon as triplet bases which encodes an amino acids other than isoleucine, M represents T or C, and the underlined bases encode the amino acid at position 213.

10. (withdrawn-currently amended): A non-human gene-mutated ~~animal~~ mouse having a mutant presenilin-2 gene which comprises a DNA having a sequence encoding a protein in which an amino acid at position 141 and/or 436 is substituted with a different amino acid in an amino acid sequence of a presenilin-2 protein.

11. (withdrawn-currently amended): The non-human gene-mutated ~~animal~~ mouse according to claim 10, wherein the ~~animal~~ mouse has the mutant presenilin-2 gene which comprises a DNA having a sequence encoding a mutant presenilin-2 protein which contains a mutation of N141I and/or M239V in the amino acid sequence of the presenilin-2 protein.

12. (canceled)

13. (currently amended) The non-human gene-mutated ~~animal~~ mouse according to claim 1, wherein the ~~animal~~ mouse can express a mutant presenilin-1 protein and wherein the expression of said protein induces the production of amyloid β protein in an amount sufficient to form a progressive neural disease in a peripheral portion of the cerebral cortex of the brain of the animal.

14. (canceled)

15. (canceled)

16. (currently amended): The non-human gene-mutated ~~animal~~ mouse according to claim 1, wherein the presenilin-1 gene is transferred by homologous recombination.

17. (currently amended): The non-human gene-mutated ~~animal~~ mouse according to claim 1, wherein amount of the amyloid protein expression in a brain tissue induced by the presenilin-1 gene is sufficient to cause affected behavior in a memory learning test in comparison with a normal ~~animal~~ mouse, and sufficient to induce abnormal neuropathy in a peripheral portion of the cerebral cortex of the hippocampus of the brain of the animal.

18. (withdrawn-currently amended): A non-human gene-mutated ~~animal~~ mouse having a DNA which comprises a mutant ~~preceilin~~ presenilin-1 gene encoding a mutant ~~preceilin~~ presenilin-1 protein in which one or two or more amino acids is substituted with a different amino acid in an amino acid sequence of presenilin-1 protein together with a DNA having a nucleotide sequence encoding a marker protein.

19. (withdrawn): A plasmid comprising a DNA or a part thereof, wherein said DNA has a sequence of a mutant presenilin-1 gene wherein a DNA sequence encoding around an amino acid at position 213 of an amino acid sequence of a presenilin-1 protein is the following sequence:

5'-TGTGGTCGGGATGATMGCC ANC CACTGGAAAGGCCC-3'

wherein N represents A, G, or C, M represents T or C, and the underlined bases encode an amino acid at position 213.

20. (withdrawn): A plasmid comprising a DNA or a part thereof, wherein said DNA has a sequence of a mutant presenilin-1 gene which encodes a mutant presenilin-1 protein wherein an amino acid at position 213 is substituted with an amino acid other than isoleucine in an amino acid sequence of a presenilin-1 protein and has a DNA sequence encoding around the amino acid at position 213 of presenilin-1 protein is the following sequence:

5'-TGTGGTCGGGATGATMGCC XYZ CACTGGAAAGGCCC-3'

wherein M represents T or C, XYZ denotes a codon as triplet bases encoding an amino acid other than isoleucine, and the underlined bases encode the amino acid at position 213.

21. (withdrawn): A chromosomal DNA containing exon 8 of a mutant presenilin-1 gene encoding a mutant presenilin-1 protein in which an amino acid at position 213 is substituted with an amino acid other than isoleucine in an amino acid sequence of a presenilin-1 protein.

22. (withdrawn): A plasmid comprising a DNA wherein a Sau3AI site is introduced into a nucleotide sequence comprising the whole or a mutated part of a cDNA or chromosomal DNA of a mutant presenilin-1 gene encoding a mutant presenilin-1 protein in which an amino acid at position 213 is substituted with an amino acid other than isoleucine in an amino acid sequence of a presenilin-1 protein.

23. (withdrawn): The plasmid according to claim 22, wherein the substitution of the amino acid is from isoleucine at position 213 to threonine.

24. (withdrawn): A plasmid comprising a DNA specified by the following nucleotide sequence:

5'-TGTGGTCGGGATGAMCGCCACCCACTGGAAAGGCCC-3'

wherein M represents T or C.

25. (withdrawn): A gene encoding a mouse mutant presenilin-1 protein wherein isoleucine at position 213 is substituted with an amino acid other than isoleucine in an amino acid sequence of a mouse presenilin-1 protein.

26. (withdrawn): The gene according to claim 25, wherein the substitution is from isoleucine to threonine.

27. (withdrawn): A plasmid comprising:

(1) a gene encoding a mouse mutant presenilin-1 protein wherein isoleucine at position 213 is substituted with an amino acid other than isoleucine in an amino acid sequence of a mouse presenilin-1 protein; and

(2) a neomycine expression unit flanked by loxPs.

28. (withdrawn): The plasmid according to claim 27, wherein the substitution is from isoleucine to threonine.

29. (withdrawn): An embryo introduced with a plasmid comprising a DNA represented by the nucleotide sequence:

5'-TGTGGTCGGGATGATMGCCACCCACTGGAAAGGCCC-3'

wherein M represents T or C.

30. (withdrawn): An embryo obtained by homologous recombination using the plasmid according to claim 1.

31. (withdrawn): The embryo according to claim 29, wherein the embryo is derived from a mammalian rodent.

32. (withdrawn): The embryo according to claim 29, wherein the embryo is an embryonic stem cell derived from a mouse.

33. (previously presented): A primary cell culture or a subcultured cell obtainable by isolating a cell from the gene-mutated animal according to claim 1 and culturing said cell by tissue culture.

34. (withdrawn): A method for producing a ~~non-human~~ gene-mutated ~~animal~~ mouse, wherein the method comprises the step of transferring a mutant presenilin-1 gene by homologous recombination into an embryo of ~~an animal~~ a mouse, wherein the mutant presenilin-1 gene is capable of expressing a mutant presenilin-1 protein and inducing production of amyloid ß protein in an amount sufficient to form a progressive neural disease in the hippocampus or a peripheral portion of the cerebral cortex of the brain.

35. (withdrawn): The method according to claim 34, wherein a mutant presenilin-1 protein is expressed in which isoleucine at position 213 is substituted with an amino acid other than isoleucine.

36. (currently amended): A method for evaluating the therapeutic effect or preventive treatment of a substance on Alzheimer's disease, which comprises:

administering a test substance to a gene-mutated ~~animal~~ mouse according to claim 1, then determining a total amount of amyloid β in the brain (M) and the amount of amyloid β 40 and amyloid β 42 in the brain, then calculating a ratio of amyloid β 42/amyloid β 40 (P);

administering a reference substance to a gene-mutated ~~animal~~ mouse according to claim 1, then determining a total amount of amyloid β in the brain (N) and the amount of amyloid β 40 and amyloid β 42 in the brain, then calculating a ratio of amyloid β 42/amyloid β 40 (Q); and

comparing the value of M to N, or the value of P to Q.

37. (original): The method for evaluation according to claim 36, wherein the comparison is conducted by using a memory learning test.

38.(original): The method for evaluation according to claim 36, wherein the comparison is conducted by using a pathological test.

39. (original): The method for evaluation according to claim 36, wherein the comparison is conducted by a pathological test based on neuropathology in a peripheral portion of the cerebral cortex.

40. (previously presented): The method for evaluation according to claim 38, wherein the comparison conducted by the pathological test based on neuropathology is a comparison of one or more items selected from the group consisting of suppression of decrease in overgrown gliosis in a peripheral portion of the cerebral cortex of the brain, suppression of decrease in uptake of 2-deoxyglucose in a peripheral portion of the cerebral cortex of the brain, and suppression of decrease in availability of 2-deoxyglucose in the cerebral cortex of the brain.

41. (original): The method for evaluation according to claim 36, wherein the comparison is conducted for one or more items selected from the group consisting of survival period of time, exploratory behavior, and migratory behavior.

42. (original): A method for evaluating a medicament for therapeutic and/or preventive treatment of Alzheimer's disease which comprises the step of culturing the primary cell culture or the subcultured cell according to claim 33 *in vitro* in the presence of a test compound.

43. (withdrawn): A method for diagnosing Alzheimer's disease or a possibility of onset of Alzheimer's disease, which comprises the use of a partial nucleotide sequence of a mutant presenilin-1 gene encoding an OS-2 type mutant presenilin-1 protein.

44. (withdrawn): A substance useful for therapeutic and/or preventive treatment of Alzheimer's disease selected by the evaluation method according to claim 36.

45. (withdrawn): A medicament for therapeutic and/or preventive treatment of Alzheimer's disease comprising the substance according to claim 44 as an active ingredient.

46. (withdrawn-currently amended): A gene-mutated ~~animal~~ mouse having a mutant presenilin gene and a gene encoding a mutant amyloid precursor protein, wherein the animal is a hybrid animal or its progeny which is produced by mating the gene-mutated ~~animal~~ mouse according to claim 1 with an ~~animal~~ mouse having a gene encoding a mutant protein of the amyloid precursor protein and high productivity of amyloid ß protein.

47. (canceled)

48. (withdrawn-currently amended): The gene-mutated ~~animal~~ mouse according to claim ~~47~~ 46, wherein the animal having a gene encoding a mutant protein of the amyloid precursor protein and high productivity of amyloid ß protein is a PS1-mutated mouse.

49. (withdrawn): A gene-mutated mouse having a mutant presenilin gene and a gene encoding a mutant amyloid precursor protein, wherein the mouse is a hybrid mouse or its progeny which is produced by mating the gene-mutated animal according to claim 7 with a mouse having a gene encoding a mutant protein of the amyloid precursor protein and high productivity of amyloid ß protein.

50. (withdrawn): A gene-mutated mouse having a mutant presenilin gene and a gene encoding a mutant amyloid precursor protein, wherein the mouse is a hybrid mouse or its progeny which is born by mating the gene-mutated animal according to claim 36 with a mouse having a gene encoding a mutant protein of the amyloid precursor protein and high productivity of amyloid ß protein.

51. (currently amended): A ~~non-human~~ gene-mutated ~~animal~~ mouse having a mutant presenilin-1 gene which encodes for the OS-2 type mutation of presenilin-1, wherein the mutant presenilin-1 gene results in overexpression of Amyloid β 42 in the brain of said mouse.